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Software as medical devices – regulatory aspects for clinical trials

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Regulatory framework

Switzerland has transposed the EU MDR into Swiss law

- EU: Medical Device Regulation (MDR)
  - Harmonized standards, non-harmonized standards, guidelines
- CH:
  - Therapeutic Products Act (TPA)
  - Medical Devices Ordinance (MedDO)
  - Ordinance on In Vitro Diagnostic Medical Devices (IvDO)
  - Ordinance on clinical trials with medical devices (ClinO-MD)

Laws, Standards in EU (Switzerland)

Requires

QMS

Usability

Risk Management

Software Lifecycle process

Defines

ISO 13485

IEC 62366

ISO 14971

IEC 62304

Suggest

Non exhaustive lists of requirements and standards!

Is software a medical device?

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Art. 1 Medical Devices

[1] Medical devices are instruments, apparatus, appliances, software, materials, accessories or other medical technology articles, whether used alone or in combination, including the software intended to be used specifically for diagnostic or therapeutic purposes and necessary for the proper application of a medical device:

a. that are intended for use on human beings;

b. that do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which action can be assisted by such means; and

c. that serve to:

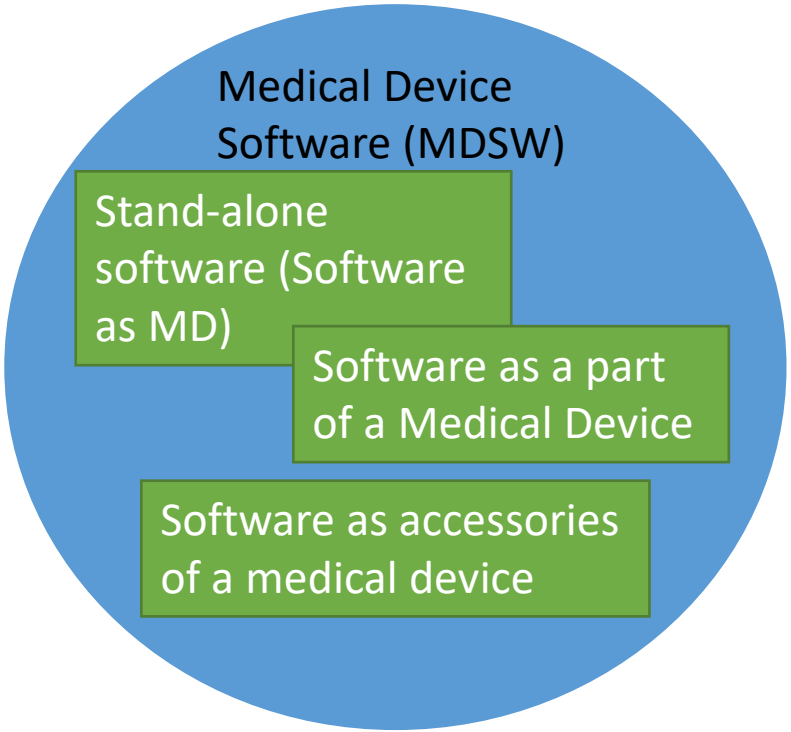
1. diagnose, prevent, monitor, treat or alleviate diseases,
2. diagnose, monitor, treat or alleviate injuries or disabilities, or compensate handicaps,
3. investigate or modify the anatomy, to replace parts thereof, or to investigate, modify or replace a physiological process,
4. control conception or to make diagnoses in relation to conception.[8]

MedDO Art. 1

Is it a medical software?

Non-medical software:

- Software only for save and display laboratory data
- Software for administrative support, e.g. management of physician visits, resources planning billing
- Electronic health records (EHR)
- Software/apps encourage a healthy lifestyle, e.g. on fitness, well-being, nutrition



Terms and definition

SaMD vs MDSW

SaMD (Software as Medical Device) / stand alone software

- “software intended to be used for one or more medical purposes that perform these purposes **without being part of a hardware** medical device“. IMDRF

MDSW (Medical Device Software)

- “Medical Device Software” is used in the EU.
- "Medical device software is software that is intended to be used, **alone or in combination**, for a purpose as specified in the definition of a “medical device” in the MDR or IVDR, regardless of whether the software is independent or driving or influencing the use of a device. MDCG Document

IMDRF: International Medical Device Regulators Forum

Is it a medical device software?

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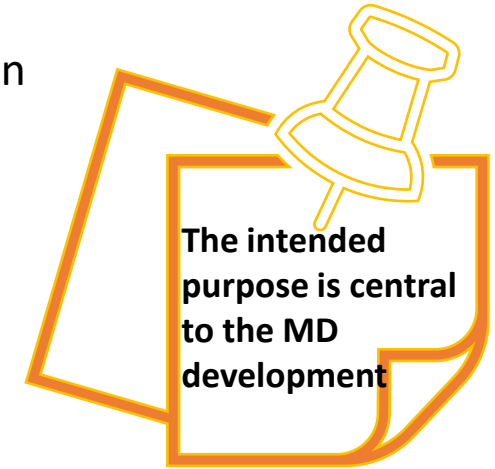
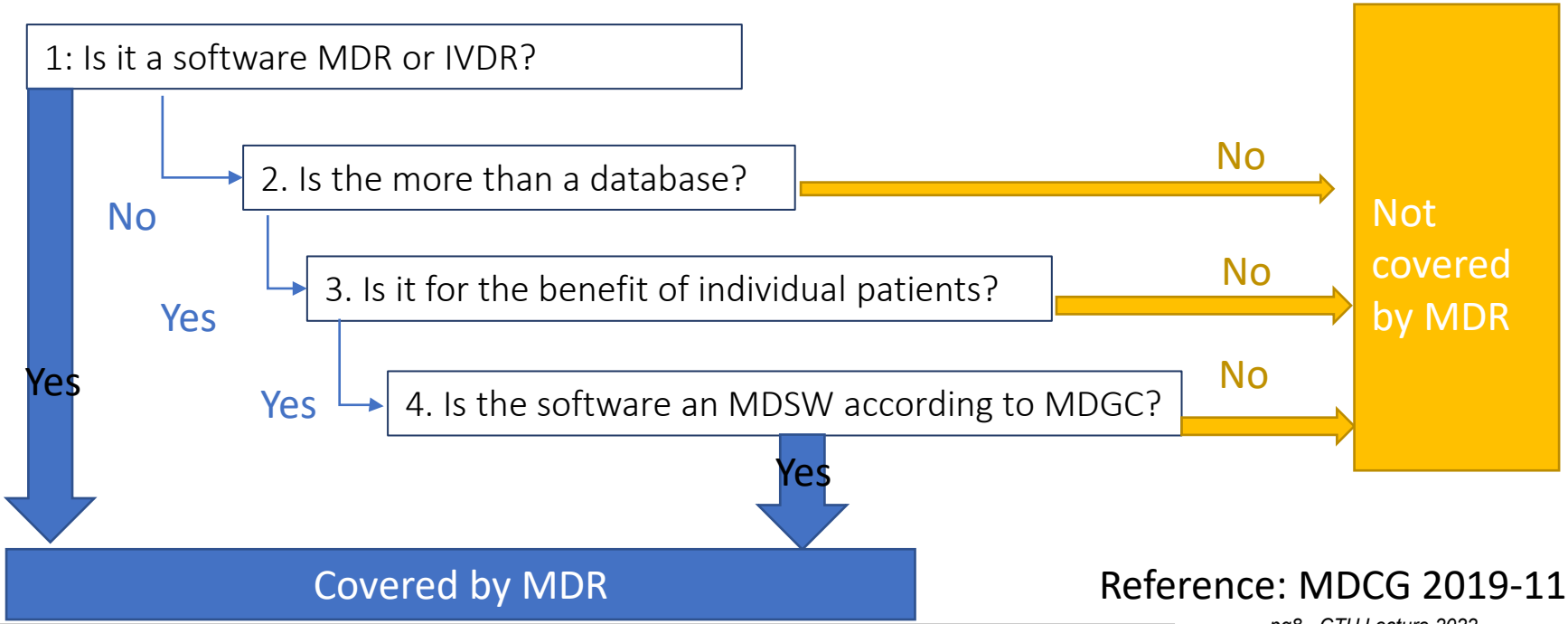
- Software must have a **medical purpose** on its own to be qualified as a medical device software (MDSW). It should be noted that the **intended purpose** as described by the manufacturer of the software is relevant for the qualification and classification of any device.
- Software which is intended to **process, analyse, create or modify medical information** may be qualified as a medical device software if the creation or modification of that information is governed by a **medical intended purpose**.



MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

Is the software covered by MDR?

Decision steps according to MDCG 2019-11



Reference: MDCG 2019-11

Type medical device software

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- Software as a part of a medical device e.g. as embedded software of a medical device
- Software as medical device (standalone software)
- Software as accessories of a medical device
- Discrete software, that is not a medical device

Manufacturer classify its own software.
Notified Bodies can provide advice.

Software as part of medical device

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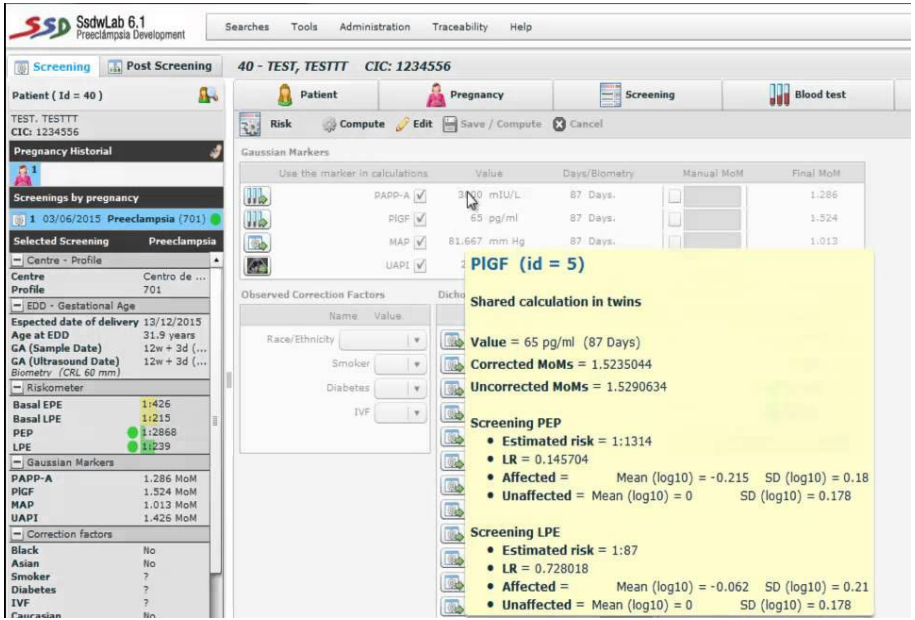
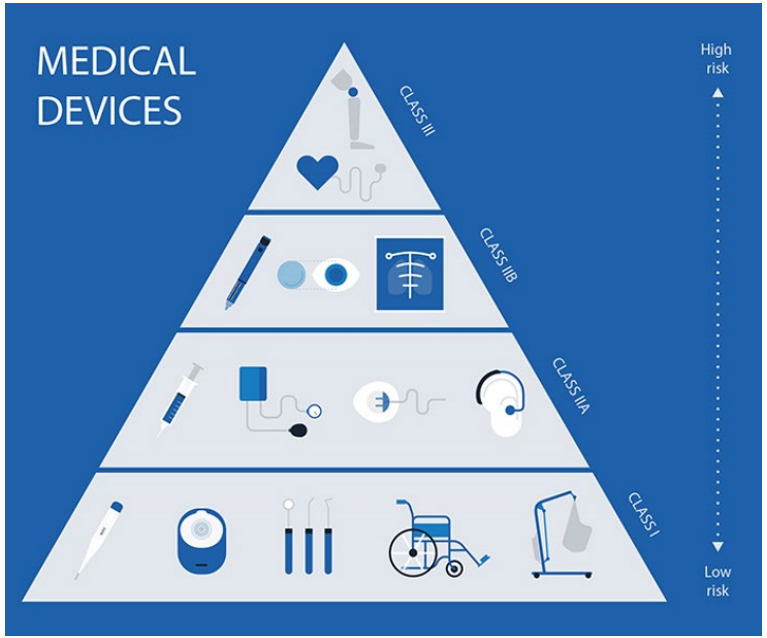
- "embedded software", "firmware
- E.g. Closed loop insulin delivery system
- Software that measure and transmit blood glucose levels, calculate insulin dose required and drive the insulin pump to administer the calculated dosage

Stand alone software

- SsdwLab 6 Prenatal Aneuploidy Screen software for evaluating the risk of trisomy 21.
- Software for surgical planning
- ECG interpretation software



Classification of Medical Devices (including software) according to MDR



Class	Conditions
III	Death or irreversible deterioration
IIb	Monitoring of vital physiological parameters that could result in immediate danger to the patient
IIa	Take decision with diagnosis or therapeutic purposes, monitor physiological processes
I	All other software

Classification according risk

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- Fertility Tracker
- Expecting a baby: Initially a Class I MD
- Use as contraception but become pregnant? Later register as Class II MD
- The risk of getting pregnant is not the same in the different senerio

Guideline for risk classification of MD
1.EU: Manual on Borderline and Classification
2.IMDRF
3.MEDDEV 2.1.6
4.……

Requirement for CE marking

based on differences between risk classes

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Table 1. Summary of differences between risk classes.

Class	Documentation	Notified body involved?	QMS[a]	Certificates	Clinical investigation
I (low risk)	Manufacturer must compile the technical documentation and self-declare conformity	No	Yes	No	Not mandatory. May be required depending on the outcome of the clinical evaluation
IIa (low-medium risk)	Manufacturer must draw up the technical documentation and apply to a European Notified Body	Yes	Yes, certified	Yes (Annex IX certificate, QMS certificate)	Not mandatory. May be required depending on the outcome of the clinical evaluation
IIb (medium-high risk)	Manufacturer must draw up the technical documentation and apply to a European Notified Body	Yes	Yes, certified	Yes (Annex IX certificate, QMS certificate)	Not mandatory. May be required depending on the outcome of the clinical evaluation
III (high risk)	Manufacturer must draw up the technical documentation and apply to a European Notified Body	Yes, expert panel	Yes, certified	Yes (Annex IX certificate, QMS certificate)	Mandatory

[a]QMS: Quality Management System.

Keutzer L. et al, 2020 doi: 10.2196/17567. PMID: 32589154

Terms & Definition: Clinical Evaluation

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- Systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the **safety and performance**, including clinical benefits, of the device when used as intended by the manufacturer. (MDR Article 2 (44))
- Clinical evaluation shall follow a defined and methodologically sound procedure based on the following:
  - Critical evaluation of the relevant scientific literature of an «equivalent» device
  - Critical evaluation of the results of all available clinical investigations
  - Consideration of currently available alternative treatment options for that purpose, if any.

Terms & Definitions

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- **Clinical trial** in Swiss legal texts is an umbrella term used for
  - Clinical investigations with medical devices (ClinOMD, MedDO)
  - Performance studies with in-vitro diagnostic (IvDO)
  - Clinical trials of medicinal products (ClinO)
  - Clinical trials conducted with other interventions (e.g. surgical interventions, other therapies
- A **clinical investigation with a medical device** is any “systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device”. (MDR Art 2(45))

Clinical investigations

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As per MDR a clinical investigation is required

- For all implantable and class III devices, with some exceptions in cases of modified devices. (Article 61(4))
- Must be conducted if there was no sufficient pre-existing clinical investigation data or scientific literature on which to base a clinical evaluation (Art 61 MDR)
- If any gaps in clinical evidence identified through a systematic scientific literature review make additional clinical data necessary to address outstanding issues. (Annex XIV Part A 1)
  - Outstanding issues E.g. : new indication, new materials, location not previously exposed, significantly longer exposure time.

Law, standards and guidance for clinical investigation

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- Law in Switzerland
  - Human Research Act, ClinO-MD, Human Research Ordinance, Ordinance on Organisational Aspects of the HRA
- Standards and Guidance
  - Declaration of Helsinki
  - ISO 14155: Clinical investigation of medical devices for human subjects - GCP
  - MEDDEV 2.7/4 - Guidelines on Clinical investigations: a guide for manufacturers and notified bodies
  - GHTF SG5/N3:2010 - Clinical Investigations
  - MDCG 2020-10/1- Safety reporting in clinical investigations ofmedical devices
  - MDCG- 2020-1 Guidance on Clinical Evaluation (MDR) /Performance Evaluation (IVDR) of Medical Device Software

Clinical investigation categorization

ClinO-MD

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Category A	**Post-market:** CE mark obtained. It is used in accordance with the instructions. The use of the MD is not prohibited in Switzerland. Approval by EC only
A1	No invasive or burdensome procedures compared to use under normal circumstances
A2	Invasive or burdensome procedures compared to use under normal circumstances
Category C	**Pre-market:** Approval by both Swissmedic and EC
C1	The medical device bears a CE-marking but it is not used in accordance with the intended purposes and the CE-marked instructions for use (off-label use)
C2	Not CE-marked
C3	Use of the medical device is prohibited in Switzerland

Submission

- Cat A: EC only
- Cat C: Submission to both EC (BASEC) and Swissmedic (eMessage) on the same day
  - C1 and C2 → Simplified review by Swissmedic
    a) noninvasive device classified as risk class I or IIa according to Art. 15 MedDO .
    b) minimal risks to the subjects.
    c) The investigators have agreed in written form to inform the Sponsor without delay of all serious adverse events or other (new) circumstances that could threaten the safety of subjects or device users according to Art. 32 ClinO-MD (see also sections 7.2.2 and 7.2.3 of this information sheet).
    d) The Sponsor has a risk management system in place to monitor safety.

Example study: OPTICA

Clinicaltrials.gov: NCT03724539

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- Aim: To assess the effect of pharmacotherapy optimization through STRIPA on the medication appropriateness, which is measured by the medication appropriateness index (MAI) for drug overuse and by the assessment of underutilization (AOU) for drug underuse.

Experimental arm	Intervention
I…ion group	Electronic- decision making assistant (STRIPA) • Recording medication and diagnoses in STRIPA • Structured drug review through the GP based on the STRIPA with the integrated STOP/START criteria • Shared decision-making between GP and patient with possible adaptation of the recommendation
Contr…	Usual medication review by their GP

Study type: Medical Device: Cat C (a) the medical device does not have a conformity marking. MDSW subject of research

Example study: DeintensiF

Clinicaltrials.gov: NCT05388136

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Aim: To determine whether an individualized FU approach to surveil patients is non-inferior to a conventional FU in head & neck cancer with regard to 5-year restricted mean survival time (RMST).

Experimental arm	Intervention
Deintensified arm	Less intense follow up visit without imaging Electronic Patient Reported Outcome (ePRO) is to be completed monthly by the participant, the PRO result will trigger an alert to the participant and to the site in conditions indicating possible relapse or second primary malignancy and recommend a follow up visit.
Co	Frequent follow up visit and imaging Electronic Patient Reported Outcome (ePRO) is to be completed monthly by the participant, no alert will be generated.

Study type: Other clinical trials, cat A. ePRO not subject of research

Requirement on clinical investigations

CE mark vs academic research

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MDSW is used in a conformity assessment by the manufacturer

° Before CE mark (MDR Art 62)

° Post Market Clinical Follow up (PMCF) investigations

SW is used in academic research project (MDR Art. 82 other clinical investigation) shall comply with the provisions of MDR Article 62 (2) and (3), points (b), (c), (d), (f), (h), and (l) of Article 62(4) and Article 62(6).

Academic research / CE Mark

Use of unapproved software in a clinical investigation

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- If a medical device is used in a research project but is **not the subject of the investigation**, it is not always a clinical study with medical devices. General requirements for clinical research applies.
- There is no data on the validity or safety of the product.

Academic Research, Basic Principles and local laws apply→ Data cannot be used for CE marking

Soley for research purposes or additional medical purpose?

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- A medical purpose exists if the data generated by the medical device influence medical decisions
- Forbidden to dispense non-compliant (non-CE certified) devices for a medical purpose (MedDO)
- If the mobile technologies are not medical devices, the data are not considered to be trustworthy for individual medical purposes

Swissmedic position paper: Decentralised clinical trials (DCTs) with medicinal products in Switzerland (Version 1.1, 25 October 2021)

Take home massage

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- The **intended purpose** of a device decides if it is a MD and its safety classes.
- The safety class of the MD decides its regulatory approval requirement.
- Clinical investigation is mandatory for all Class III MD and may be required for MD of other classes depending on the result of the clinical evaluation.
- Clinical investigation study type depends on whether the MD is CE marked and the **subject of the investigation**.
- Only data generated from a MD is considered trustworthy for medical purposes.

Thank you!